

**UNITED STATES DISTRICT COURT
DISTRICT OF NEW JERSEY**

GRÜNENTHAL GMBH, and DEPOMED,
INC.,

Plaintiffs/Counterclaim
Defendants,

v.

ACTAVIS ELIZABETH LLC and ALKEM
LABORATORIES LIMITED,

Defendants/Counterclaim
Plaintiffs.

Civil Action No. 2:13-cv-04507 CCC-MF

AND CONSOLIDATED CASES

Civil Action No. 2:13-cv-06929 CCC-MF
Civil Action No. 2:13-cv-07803 CCC-MF
Civil Action No. 2:14-cv-03941-CCC-MF
Civil Action No. 2:14-cv-04617-CCC-MF
Civil Action No. 15-cv-06797-CCC-MF

DEFENDANTS' POST TRIAL BRIEF

FILED UNDER SEAL

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This case is but a part of Plaintiffs' strategy to maintain and extend their patent monopoly relating to a particular class of opioid analgesics. In the 1970s, Plaintiff Grünenthal had invented an opioid called tramadol. That product was unique among analgesics, and the first to provide analgesic (pain-relieving) properties through an atypical combination of opioid and non-opioid mechanisms of action. Tramadol has been on the market for many years, and its atypical combination of mechanisms of action has long been known and described in the prior art.

In the late-1980s and early-1990s, Grünenthal, knowing its tramadol patent monopoly was facing worldwide expiration, initiated the "Tramadol Successor Project" to develop a new analgesic using tramadol as the starting point. Tapentadol hydrochloride was the result of the "Tramadol Successor Project" and is the subject of the '593 patent. Grünenthal later obtained the '364 patent on the most stable crystalline form of tapentadol hydrochloride and the '130 patent on treating polyneuropathic pain, a form of pain already known to be treated by tramadol.

Defendants have offered clear and convincing evidence at trial that the asserted claims in each of these patents are invalid, and that they do not induce or contribute to infringement of the '130 patent. In doing so, Defendants will demonstrate that Plaintiffs have unfairly and improperly sought to extend their patent monopoly and to forestall competition.

I. U.S. PATENT RE39,593

A. Chemical Obviousness of the Asserted Claims Under 35 U.S.C. § 103

The story of tapentadol is a continuation of the story of Grünenthal's pioneering opioid analgesic tramadol.¹ As the patent life on tramadol was expiring in the late 1980's and early-1990's, Grünenthal initiated its "Tramadol Successor Project" to develop a next-generation tramadol analog which maintained tramadol's unique mixed opioid/non-opioid mechanism of

¹ All emphasis is added unless stated otherwise.

action and retained the key chemical structure of tramadol responsible for its analgesic action. (FOF 13). Tapentadol is the obvious result of the “Tramadol Successor Project.”

1. The Law of Chemical Obviousness

The Federal Circuit has established a “lead compound” analysis for determining obviousness of chemical compounds. *See, e.g. Takeda Chem. Indus., Ltd. v. Alphapharm*, 492 F.3d 1350 (Fed. Cir. 2007). The Federal Circuit has stated that:

Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (e.g., a lead compound) to arrive at a claimed compound with a reasonable expectation of success that the new compound would have similar or improved properties compared with the old.

Daiichi Sankyo Co. v. Mylan Pharma., 619 F.3d 1346, 1352 (Fed. Cir. 2010) (citing to *Takeda* and *Eisai*). There is no requirement that the prior art direct a POSA to a single lead compound, since this would be an impermissibly “rigid” requirement. *See, Altana Pharma AG v. Teva Pharmaceuticals USA, Inc.*, 566 F.3d 999, 1008 (Fed. Cir. 2009)(affirming evidence of selection of 18 lead compounds)(“to the extent Altana suggests that the prior art must point to only a single lead compound for further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in *KSR* (citation omitted)”).

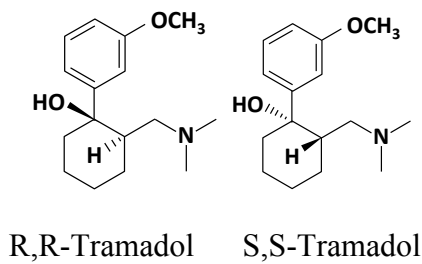
Thus, there is a two-step process for proving obviousness of a chemical compound: (1) a POSA must have some reason to select a particular prior art compound for further modification; and (2) the prior art must motivate a POSA to make the structural modifications to the lead compound to arrive at the claimed compound. As with all invalidity, the accused infringer must show these elements by clear and convincing evidence.

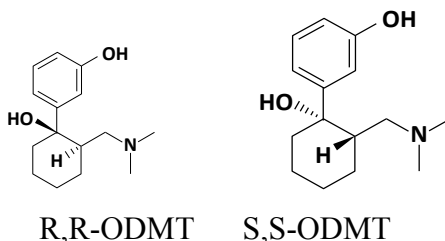
2. Person of Ordinary Skill in the Art

A POSA is a hypothetical person who is presumed to be aware of all pertinent art, thinks along conventional wisdom in the art, and is a person of ordinary creativity. With respect to the '593 patent, a POSA would have had education and/or experience in a field related to the design and synthesis of analgesic compounds, including the fields of organic chemistry, medicinal chemistry and pharmacology, and knowledge of the scientific literature concerning the design and synthesis of organic compounds used for the treatment of pain, including opioid analgesic and opioid analogs for the treatment of pain as of July 1994. The education and experience levels of a POSA would be a person holding a Ph.D. and having 3–5 years of experience in the design and synthesis of analgesics, including opioid analgesics. (FOF 7-8).

3. Selection of Tramadol or *O*-Desmethyltramadol as a Lead Compound

A POSA would have been motivated to select either tramadol or its metabolite *O*-desmethyltramadol as a lead compound for further development of an analgesic. (FOF 9-43). Tramadol is an opioid-based analgesic used to treat moderate-severe pain, and as early as 1978 its structure-activity relationships had been studied extensively and reported in the prior art. (FOF 22, 45-62). Tramadol was an approved analgesic in Europe and had been described as safe and effective in the literature based on clinical trials in humans. (FOF 12). Tramadol is a mixture of two enantiomers and it is metabolized to a mixture of two enantiomers of *O*-desmethyltramadol (ODMT).





(FOF 21).

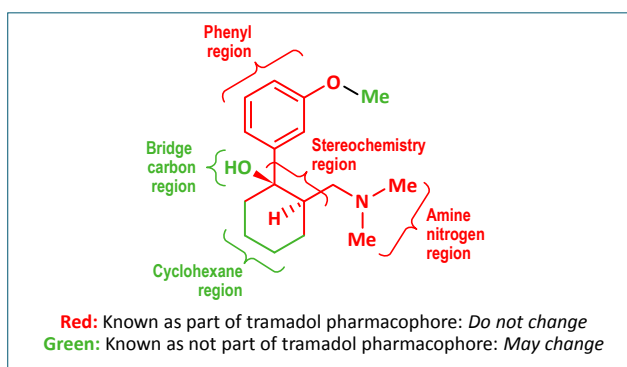
A POSA would have understood that tramadol was unique among centrally acting strong analgesics. (FOF 11, 15-20, 36-38). Prior art clinical and non-clinical data described that the analgesic activity of tramadol was atypical, deriving “from the combined contributions of an opioid and nonopioid component, without a similarly interactive combination of side effects.” (FOF 18). The polypharmacology of tramadol was reported as “unique” and “atypical” among analgesics, which translated into effective pain relief without the side effect profile of pure opioid agonists. (FOF 15-19). Hence, a POSA would have naturally selected tramadol and its metabolite *O*-desmethyltramadol as lead compounds for further modification. (FOF 20, 39). Further, a POSA would want to maintain and/or enhance these “unique” and “atypical” activities. (FOF 20, 39).

The atypical analgesic activity of tramadol, including the combined contributions from opioid and nonopioid components, was known to involve both (+)- and (–)-tramadol, as well as their corresponding metabolites (+)- and (–)-*O*-desmethyltramadol. (FOF 36-38). (–)-tramadol was believed to contribute to tramadol’s antinociceptive (analgesic) properties via α_2 -adrenoreceptors, whereas (+)-*O*-desmethyltramadol was believed to contribute via mostly μ -opioid receptors. (FOF 36-38). The effects of both (+)-tramadol and (–)-*O*-desmethyltramadol were believed to consist of combined μ -opioid and α_2 -adrenergic components. (FOF 36-38).

A POSA would have been motivated to select the (+)/(-)-tramadol racemate, the (+)/(-)-*O*-desmethyltramadol racemate, or each of the individual stereoisomers (+)-tramadol, (-)-tramadol, (+)-*O*-desmethyltramadol, and (-)-*O*-desmethyltramadol as lead compounds, given the known contribution of each to the analgesic action of tramadol. (FOF 39). A POSA would have known that the effects of both (+)-tramadol and (-)-*O*-desmethyltramadol consisted of combined opioid and non-opioid components and would have had a particular interest in the metabolite (-)-*O*-desmethyltramadol because it was known to be more active and would avoid any complications associated with poor liver metabolism in certain patients. (FOF 23-26, 39). Taking the prior art as a whole, a POSA would have been motivated to select (-)-*O*-desmethyltramadol as a lead compound. (FOF 39).

4. Motivation to Modify Lead Compound

Based on the known structure-activity relationships of tramadol, a POSA would have expected that certain structural aspects of tramadol known to be important for its analgesic activity (*i.e.*, the tramadol pharmacophore) would not be promising structural features for modification. (FOF 44-62) Shown in in red in the structures and drawings depicted below:



A POSA would have expected from the prior art that the features shown above in green would be promising for modification, without disrupting the pharmacophore. (FOF 62-63).

a. **A POSA Would Not Change the Known Tramadol Pharmacophore**

(1) **The Dimethylaminomethyl Group**

It was known that the dimethylaminomethyl [$-\text{CH}_2-\text{N}(\text{CH}_3)_2$] feature of tramadol (the “amine nitrogen region,” see above) significantly interacted with the opioid receptor. A POSA would not be motivated to make a change to this feature of the lead compounds. (FOF 48-50).

(2) **Aromatic Oxygen Substituent**

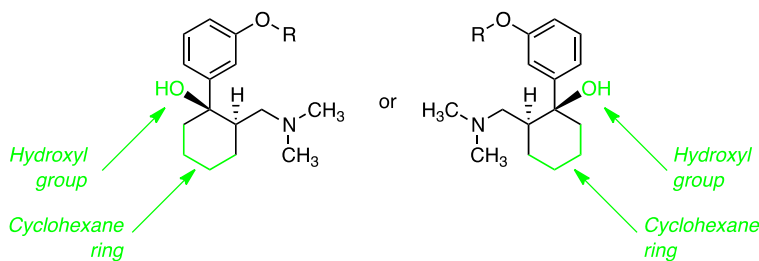
A POSA would not be motivated to remove or alter the meta-hydroxy group (the O-Me group in the figure above) in tramadol or *O*-desmethyltramadol. (FOF 51-54).

(3) **Relative Stereochemistry**

The preferred stereochemistry for tramadol was well established in the prior art. (FOF 57). Thus, in terms of relative stereochemistry, a POSA would have been motivated to design tramadol analogs having the same stereochemical relationships as tramadol. (FOF 57-59).

b. **Tramadol Features for Possible Modification**

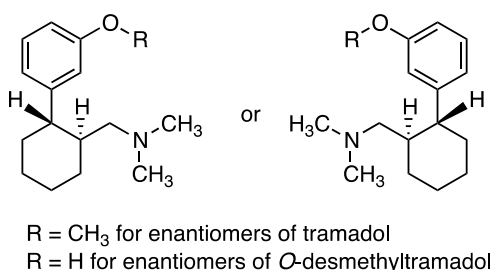
A POSA would have considered two features as most promising for possible modification that would reasonably lead to new compounds having similar or improved analgesic activity: these are the bridge-carbon hydroxyl group and the cyclohexane ring. (FOF 62-63).



R = CH₃ for enantiomers of tramadol
R = H for enantiomers of *O*-desmethyltramadol

(1) Bridge-Carbon Hydroxyl Group

A POSA would be motivated to replace the bridge carbon -OH with a -H to simplify the molecule, in keeping with the opioid tradition of simplifying analgesics based on morphine. (FOF 64-66). The same change had already been made and described in the 1978 structure-activity study paper by *Flick*, the inventors of tramadol, and the authors were surprised that the compound with the -H at the bridge carbon retained strong analgesic activity, and that would have been important to a POSA. (FOF 55-56, 64-66). A POSA would have had a reasonable expectation that the resulting compounds (shown below) would possess analgesic activity. (FOF 55-56, 64-66).

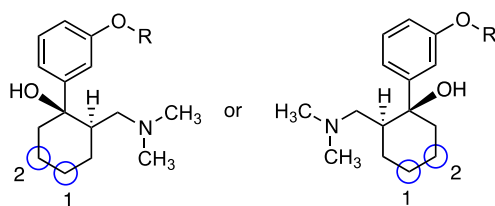


(2) Cyclohexane Ring

Based on the prior art, a POSA would not have expected that expanding or contracting the cyclohexane ring, or adding substituents to that ring, would have led to an analgesic compound with similar or improved properties compared to tramadol. (FOF 60-61).

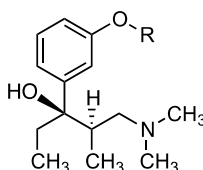
Another possible modification of the cyclohexane ring involves preparing a ring-opened compound to give “open chain” or “linear” analogs of tramadol or *O*-desmethytramadol that would be somewhat more flexible than tramadol. A POSA would have expected that making more flexible analogs of tramadol would be an attractive option, because such compounds might reasonably be expected to adopt conformations that would enable optimal interactions, and thus enhanced binding, at both non-opioid and opioid receptors. (FOF 67-78).

The most promising option for modifying the cyclohexane ring would be to eliminate one or two of the carbon atoms of the cyclohexane ring encircled in blue as 1 or 2 below (*Excision*). (FOF 4-75). Between the two “excision” possibilities noted below by blue circles, making an “open chain” analog by eliminating the $-(CH_2)-$ group labeled as 1 above would provide “open chain” compounds of the general structure depicted below for (+)-tramadol and (+)-*O*-desmethytramadol (FOF 75):



R = CH₃ for enantiomers of tramadol

R = H for enantiomers of *O*-desmethytramadol



R = CH₃ for (+)-tramadol derivative

R = H for (+)-*O*-desmethytramadol derivative

Compounds closely related to these “open chain” analogs of (+)-tramadol and (+)-*O*-desmethytramadol were known in the prior art. (FOF 71).

It was also known prior to July 1994 that “open-chain” analogs of tramadol and *O*-desmethytramadol closely related to the acyclic structures shown above possessed pharmacological activity, including analgesic, anesthetic, antidepressant, and antispasmodic activity. (FOF 76-77). By “excising” a $-(CH_2)-$ group in this way, a POSA would have had a reasonable expectation that the resulting compounds would possess pharmacological activity, including similar or improved analgesic activity, compared to tramadol and *O*-desmethytramadol. (FOF 77-78).

c. Salt Selection

The pharmaceutically acceptable salts of tramadol and *O*-desmethyltramadol, including the hydrochloride salts, were known in the art prior to July 1994 as the preferred forms. (FOF 79). The hydrochloride salt of tapentadol would have been obvious for the same reasons discussed above. (FOF 79). Salt forms of active pharmaceutical ingredients were common as of July 23, 1994 and hydrochloride salts of APIs were common as of the early 1990's—indeed the hydrochloride was the most common salt. (FOF 79).

Finally, and as discussed above, a POSA would have been motivated to begin with each of the individual stereoisomers (+)-tramadol, (–)-tramadol, (+)-*O*-desmethyltramadol and (–)-*O*-desmethyltramadol as lead compounds, and, as discussed above, would have been particularly interested in (–)-*O*-desmethyltramadol. (FOF 39). A POSA motivated to make the design modifications to (–)-*O*-desmethyltramadol described above, and with the expectation that the final compound should retain the important absolute stereochemical relationships in (–)-*O*-desmethyltramadol, would arrive at tapentadol as an isolated enantiomer. (FOF 77, 82).

5. Synthesis of Tapentadol Hydrochloride

It would have been only a matter of routine experimentation for a POSA to synthesize tapentadol and its pharmaceutically-acceptable salts, including tapentadol hydrochloride. (FOF 80). The synthesis of tapentadol can be achieved using routine, well-known reactions that are taught in undergraduate and first-year graduate organic chemistry courses and would have been apparent to a POSA by July 1994. (FOF 80).

6. Method Claims 8 and 117

Claims 8 and 117 of the '593 patent recite “[a] method of treating a mammal suffering from pain” by administering either tapentadol hydrochloride. The use to treat pain was obvious from the very pharmaceutical context in which a POSA would have approached the project, and

does not impart a valid patentable distinction to a “method of treating pain.” (FOF X).

7. **There are no Surprising or Unexpected Results**

Because tapentadol was designed with tramadol in mind, it can hardly have been surprising or unexpected that tapentadol possessed a mixed opioid/non-opioid mechanism of action. (FOF 83). A POSA would have known and understood that both (+)-tramadol and (–)-O-desmethyiltramadol, each a single molecule, had a dual μ -opioid and noradrenergic (*i.e.*, norepinephrine) mechanism of action, both important mechanisms for analgesia, and that it was possible for a single molecule to have these dual pharmacological properties. (FOF 36-38).

Opening the rigid cyclohexane ring of tramadol or *O*-desmethyiltramadol would not have been expected to produce a flexible molecule that would be less likely to functionally bind to the *in vivo* receptors needed for biological activity. (FOF 70,78). Plaintiffs offered no evidence that there is a general rule dictating that more flexible open-chain analogs of cyclic molecules will have reduced or eliminated biological activity.

B. The Asserted Claims Lack Utility Under 35 U.S.C. § 101 and § 112/1

A “patent may not be granted to an invention unless substantial and practical utility for the invention has been discovered ***and disclosed.***” *Fujikawa v. Wattanasin*, 93 F.3d 1559, 1563 (Fed. Cir. 1996).² Utility is determined from the objective perspective of a POSA as of the purported effective filing date. *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1323-24 (Fed. Cir. 2005). In the chemical arts, the utility inquiry focuses on the “***desired [pharmacological] response***” for the invention. *Fujikawa*, 93 F.3d at 1564. “[T]esting is often required to establish practical utility” and must be “***reasonably indicative of the desired [pharmacological] response.***” *Id.* “[T]here must be a ***sufficient correlation*** between the tests

² Failure to meet the utility requirement of § 101 also means failure to meet the “how to use” requirement of § 112/1. *Rasmusson*, 413 F.3d at 1323. (COL 501.)

and an asserted pharmacological activity so as to *convince those skilled in the art*, to a *reasonable probability*, that the novel compound will exhibit the asserted pharmacological behavior.” *Fujikawa*, 93 F.3d at 1564 (italics in original). (COL 501-508.)

1. **The Specification Contains No Testing About the “Desired Pharmacological Response”**

The asserted claims lack utility because the specification undisputedly contains no testing to support the “*underlying object of the present invention*,” which was to “provide substances with an analgesic effect, which are suitable for the treatment of severe pain *without giving rise to the side effects which are typical of opioids*.” (FOF 505-508.)³ At trial, Plaintiffs sought to evade the specification’s recitation of the desired pharmacological activity. But Dr. Roush conceded the statement about side effects *is* the asserted utility. (FOF 505.) And Dr. Ossipov confirmed that the “underlying object of the present invention” refers to what the inventors hoped to achieve. (*Id.*) As of 1994, animal models to assess opioid side effects were known, but the ’593 patent undisputedly contains *none*. (FOF 507.) For this reason alone, a POSA would conclude that the asserted claims lack utility as analgesics without opioid side effects. (FOF 501-508; COL 514.)

2. **The Specification Does Not Establish Even Merely Analgesia**

Plaintiffs urge that the asserted utility is mere analgesic activity.⁴ Even so, the asserted claims still fail the utility test. Preliminarily, the specification undisputedly contains *no testing* of any kind regarding the compound of Example 25, which is tapentadol. (FOF 509.) As to claims 61, 117, and 147, which are specifically directed to the tapentadol species, that is dispositive.

³ See FOF 501-504 regarding the testimony of Dr. Christian Wolf and Dr. Jeffrey Mogil.

⁴ Plaintiffs argue that the asserted claims do not contain language about side effects or comparisons to tramadol. But the asserted utility is a question of fact based on how a POSA understands *the specification*. *In re ’318 Patent Litig.*, 583 F.3d 1325-26 (Fed. Cir. 2009). (COL 501-508.) Claim 61 and 147 do not even include the word “analgesic.” (FOF 509.)

(COL 514.) In response, Plaintiffs ask the Court to find a POSA would *infer* analgesia based on the specification's testing of a small number of compounds using solely the mouse writhing test. That fails for two fundamental reasons.

First, while in limited circumstances, “a particular pharmacological activity identified with *prior art compounds*” may be “probative” as to the activity of structurally similar novel compounds, that doctrine is inapplicable here. *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985). Plaintiffs attempt to rely on compounds they purport were *not* known in the prior art. (FOF 513; COL 509-512.) And a POSA could draw no conclusions about the claimed compounds based on the few identified in the specification because even the most structurally similar compounds (*i.e.*, enantiomers) can have profoundly different activities. (FOF 512.) A POSA would not conclude that the claimed compounds would have analgesic activity *absent empirical data* about each one. (FOF 510-513.)

Second, the record overwhelmingly establishes that a POSA knew as of 1994 that the mouse writhing test, on its own, was not “reasonably predictive” of analgesia. (FOF 514-532.) Thus the data in the specification would not “convince [a POSA], to a *reasonable probability*” that even the few compounds tested in the specification were analgesics. *Fujikawa*, 93 F.3d at 1564. (COL 508, 514.) A body of scientific literature shows a POSA's understanding about the validity of animal tests of analgesia. (FOF 517-532.) As reflected in Dr. Hammond's authoritative chapter from 1989, “*no model is reliably predictive*” on its own, and the “inference of pain and its modulation” could be made “*only* through the judicious use of *complementary models* of nociception *and* assessments of motoric function.” (FOF 517.) The specification's lone data from the writhing test would not have persuaded a POSA that the claimed compounds had efficacy as analgesics. (FOF 518; COL¶ 514.)

Further, a POSA knew that the writhing test had several confounding effects, necessitating convergent data from multiple models. (FOF 519-532.) *First*, the writhing test was known to be non-specific, meaning that compounds known not to be analgesic nonetheless could produce a reduction in writhing. (FOF 520-524.) *Second*, the writhing test was known to be overly sensitive and confounded by stress-induced analgesia. (FOF 525-526.) *Third*, mice could exhibit decreased writhing due to motor impairment or sedation, rather than actual analgesia. (FOF 527.)

On cross, Dr. Ossipov acknowledged literature criticizing the writhing test as “not a valid animal model of” nociceptive pain and that it “is *nonspecific* and is *not reliable for predicting the analgesic activity of new compounds*, since many types of drugs are active in the test.” (FOF 528-529.) Thus, a POSA would not conclude, to a “reasonable probability,” that the claimed compounds would have efficacy as analgesics. *Fujikawa*, 93 F.3d at 1564. (FOF 514-532.)

Dr. Ossipov also admitted that the writhing test suffers from the additional limitation that it does not evoke a consistent painful noxious stimulus, including in human subjects. (FOF 528). This case thus presents a unique circumstance in which the body of scientific literature (including DTX 1576, DTX 97, and DTX 2057) expressly documents that, as of 1994, a POSA knew the writhing test was not “reasonably indicative” of even mere analgesic efficacy of a supposedly new compound. *Fujikawa*, 93 F.3d at 1564. (FOF 528-529.) Given that objective legal standard, Defendants have demonstrate clear and convincing evidence of lack of utility (and ensuing lack of a July 23, 1994 priority date, *see supra*). (COL 514.)

Dr. Ossipov’s own actions speak much louder than his words. In his long career as the self-described “animal models person,” (FOF 530), *he has never used the writhing test in any of his publications* – let alone as the sole basis to conclude that a new compound was an analgesic.

(FOF 530-531.) Dr. Ossipov’s scientific publications are entirely consistent with Dr. Mogil’s and Dr. Hammond’s precepts that “no final conclusions” regarding analgesia can be reached on the basis of one model alone. (FOF 532.) Dr. Ossipov’s testimony that the Patentees here “were not making a firm conclusion,” but merely disclosing “the beginning of a study” is irrelevant. (*Id.*) Utility requires more than “simply an object of research.” *In re ’318 Patent Litig.*, 583 F.3d at 1324. (COL 514.)

3. **Plaintiffs May Not Rely On Post-Filing Data To Support Utility**

The prosecution history is irrelevant to the utility inquiry because Defendants have mounted a serious challenge to the priority date by showing a POSA would *not* conclude that the asserted claims had utility based on the specification of the original application. *See Rasmusson*, 413 F.3d at 1320, 1322. (FOF¶ 533; COL¶¶ 510-513.)

4. **The Earliest Possible Priority Date is October 24, 2005**

Even if the Court were to consider post-filing data, the earliest possible priority date for the asserted claims would be October 24, 2005 after the filing of the Strassburger Declaration. (FOF 535; COL 515.)⁵ At that time, the Patentees submitted test data from multiple widely-known animal models, thereby confirming Dr. Mogil’s testimony that no single animal model was reliably predictive. (FOF 534-538.) And 50 of those data sheets – including 4 related to BN200 (tapentadol) – were dated *after* July 1994 and indisputably not available to a POSA as of the challenged 1994 priority date. (FOF 535.) Moreover, the Declaration was not in response to any request or Office Action from the PTO. (FOF 537.) The rational inference is that Grünenthal attempted to rectify glaring deficiencies in the specification. (FOF¶ 538.)

⁵ The November 24, 1997 Buschmann Declaration has several deficiencies and would not establish the requisite utility to a POSA. (FOF ¶540-543.)

C. Plaintiffs Did Not Rebut Obviousness As Of October 2005

If the Court were to rely on the October 2005 submission, the asserted claims would still be invalid because, by 2002, tapentadol was disclosed to be an “analgesic,” and Dr. Wolf detailed how that rendered the asserted claims obvious. (FOF 544-551; COL 515.) Despite over 11 million of compounds in claim 8, this 2002 reference disclosed none but tapentadol. (FOF 545.) Plaintiffs failed to rebut Dr. Wolf’s testimony on obviousness. (COL 516.)

D. Claims 61, 117, and 147 Lack Written Description Under 35 U.S.C. § 112/1

The specification must “reasonably convey to [a POSA] that the inventor had possession of the claimed subject matter *as of the filing date.*” *Ariad Pharm. Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc). “[T]he test requires an objective inquiry into the four corners of the specification from the perspective of a [POSA].” *Id.*; *see also In re Smith*, 481 F.2d 910, 914 (C.C.P.A. 1973). Where – as here – the “record then features *conflicting evidence* about the reading a [POSA] would give [to the specification],” a finding that the specification lacks an adequate written description is appropriate. *Eli Lilly & Co. v. Teva Pharm. USA, Inc.*, 619 F.3d 1329, 1345 (Fed. Cir. 2010). (COL¶¶ 517-521.)

1. The Specification Does Not Convey Possession

The record establishes numerous irreconcilable discrepancies about the identity of the compound of Example 25 in the specification. (FOF 552-560.) From these, a POSA would conclude the inventors did not know what they possessed, let alone the ultimately claimed (1R, 2R) species. (*Id.*; COL 522.) Critically, the “lead inventor” of the ’593 patent, Dr. Buschmann, admitted he initially did not know what compound he had made. (FOF 552.) Grünenthal internally determined its structure using routine techniques (FOF 533), but *never disclosed* any such structural data for a POSA to assess in the ’593 patent, (FOF 554). That is dispositive. (COL 522.)

Moreover, in the '364 patent specification, the inventors acknowledged that the original '737 patent fails to disclose the (1R, 2R) species. (FOF 555.) Only *in 2004* did the Patentees finally publicly “*prove*” to a POSA that the chemical structure depicted under Example 25 in the '737 patent “is correct” using XRPD. (FOF 556.) That action confirms Dr. Wolf’s testimony that a POSA would *require* data to prove what was purportedly synthesized. (FOF 557.)

Plaintiffs argue that the Court’s claim construction of the “(–21)” limitation should end the inquiry. (ECF No. 333 at 2.) But, as Dr. Roush acknowledged, the Court’s construction requires “*the compound*” that is depicted in the formula, not only the formula, itself. (FOF 559, 502.) Plaintiffs’ argument ignores the requirement to assess the specification *as a whole* from a POSA’s *objective scientific perspective*. *Ariad Pharm. Inc.*, 598 F.3d at 1351. (FOF 559.) Plaintiffs’ argument that a POSA could synthesize the claimed (1R, 2R) species is also misguided as there is no dispute that chemical synthesis is unpredictable, and a host of factors can cause even known chemical reactions to yield products other than expected. (FOF 560.)

2. The Prosecution History Does Not Convey Possession

Even if the prosecution history were relevant to written description (it is not), it is as confused as the specification. (FOF 561-566.) The inventors repeatedly amended the stereochemical disclosure of Example 25, each time telling a POSA the information was “true” and “correct,” and rooted in the chemical structure depicted. Yet it is undisputed that Example 25 did not contain the (1R, 2R) disclosure until July 2003. (*Id.*) These facts are clear and convincing evidence that the structure alone would have conveyed possession. *Ariad Pharm. Inc.*, 598 F.3d at 1351; *In re Smith*, 481 F.2d at 914. (COL 523.)

E. Claims 61, 117, and 147 Fail the Original Patent Rule (35 U.S.C. § 251(a))

For a reissue patent, “the [*original parent*] *specification* must *clearly and unequivocally* disclose the newly claimed invention as a separate invention.” *Antares Pharma, Inc. v. Medac*

Pharma Inc., 771 F.3d 1354, 1362 (Fed. Cir. 2014). In *Antares*, the Federal Circuit affirmed a finding of invalidity because, even though the safety feature at issue was described in the specification, “the **particular** combinations of safety features claimed on reissue [were not] disclosed in the specification.” *Id.* at 1363. That principle controls here. (COL 524-529.)

The specification of the original ’737 patent does not disclose the (1R, 2R) tapentadol species that is the subject of reissue claims 61, 117, and 147. Instead, in the ’737 patent, Example 24 discloses a (1S, 2R) compound and Example 25 discloses a (1R, 2S). (FOF 567-569.) Named inventor, Dr. Buschmann, agreed that “that there was a contradiction between the structure and the stereochemistry that’s designated” in Example 25 of the ’737 patent. (*Id.*) The experts agree that in light of this contradiction, the (1R, 2R) species was not “clearly and unequivocally” disclosed in the original ’737 patent specification. *Antares*, 771 F.3d at 1362. (*Id.*) Grünenthal even touted the absence of a disclosure of tapentadol in the ’737 patent in responding to the Examiner’s rejection of the ’130 patent application. (*Id.*) The species claims are invalid for this reason. *Antares Pharma, Inc.*, 771 F.3d at 1362. (COL 529.)

F. Genus Claim 8 Is Not Enabled Under 35 U.S.C. § 112/1

“Claims are not enabled when, at the effective filing date of the patent, one of ordinary skill in the art could not practice their full scope without undue [*i.e.*, **excessive**] experimentation.” *Wyeth v. Abbott*, 720 F.3d 1380, 1384 (Fed. Cir. 2013). As in *Wyeth*, the dispositive issue here is that a POSA must engage in “***synthesizing and screening each***” of the more than **11 million** compounds encompassed by claim 8. (FOF 572, 576; COL 530-534.) There is no dispute that this process would require an excessive amount of work (even if routine). (FOF 570-578.) Plaintiffs’ argument that synthesizing and assaying **any single one** of those millions of compounds would be a manageable amount of routine work flips the requirement to enable the **full scope** on its head. *Wyeth*, 720 F.3d at 1382. (COL 530-534.)

II. THE CLAIMS OF THE '364 PATENT ARE ANTICIPATED BY THE '737 PATENT

Asserted claims 1-3 and 25 of the '364 patent are invalid because they are anticipated by prior art patent 6,248,737 (“the '737 patent”), which reissued as Reissue Patent No. RE39,593 (“the '593 patent”). Example 25 of the '737 patent describes a procedure for making tapentadol hydrochloride crystals that inevitably results in at least some Form A. The '737 patent also discloses using Form A tapentadol in a pharmaceutical dosage, as required by claim 25. ('737 patent at 5:44-61.) The evidence therefore proved that every limitation of the asserted claims is described in the '737 patent either expressly or inherently. *See* 35 U.S.C. § 102; *Am. Calcar, Inc. v. Am. Honda Motor Co.*, 651 F.3d 1318, 1341 (Fed. Cir. 2011) (holding that a patent claim is not valid if each element is taught, whether expressly or inherently, in a single prior art reference).

A. **Following the prior art procedure in Example 25 invariably leads to Form A.**

Under 35 U.S.C. §§ 102 (a) and (b), “a [claim] limitation or the entire invention is inherent and in the public domain if it is the ‘natural result[] flowing from’ the explicit disclosure of the prior art.” *Schering Corp. v. Geneva Pharm., Inc.*, 339 F.3d 1373, 1379 (Fed. Cir. 2003), quoting *Eli Lilly & Co. v. Barr Labs., Inc.*, 251 F.3d 955, 970 (Fed. Cir. 2001). Scientists at the University of Wisconsin (“WI”) independently reproduced Example 25 and confirmed that following the prior art recipe results in at least some Form A. This is consistent with the chemical reality that Form A is the more stable at room temperature, and therefore room temperature processes of making a “crystalline” tapentadol (as the '737 patent disclosed) would naturally result in Form A. FOF 1006-1024. Further, Plaintiffs themselves admitted in the '364 patent that tapentadol “prepared according to example 25” referred to work that SSCI did, which contemporaneous documents demonstrate used Form A tapentadol. *See* Section II.A.3.

1. The Wisconsin reproduction resulted in Form A.

When the University of Wisconsin reproduced Example 25, they obtained Form A crystals of tapentadol hydrochloride. FOF 1023-1024. Defendants' polymorph expert, Dr. Jonathan Steed, reviewed the X-ray powder diffraction ("XRPD") pattern for the Wisconsin product and confirmed that it shows Form A. FOF 1024. Plaintiffs' polymorph expert, Dr. Joel Bernstein, reviewed the same XRPD pattern and admitted that the "synthesis that the University of Wisconsin conducted resulted in at least some form A." FOF 1024.

2. The Wisconsin reproduction faithfully followed Example 25.

Example 25 consists of three steps. Each step involves a particular chemical transformation that starts with a particular purified material. FOF 1008. Example 25 has one and only one step during which tapentadol hydrochloride is made: the "3rd Step." FOF 1009-1011. That is also the only step in which tapentadol hydrochloride crystals are formed. (FOF 1011.

Just as the "3rd Step" requires, the Wisconsin scientists used the starting material known as the "(-23)" compound. FOF 1012-1013. The nature and purity of the starting material was confirmed by the supplier's certificate of analysis, as well as by the WI scientists. *Id.* The Plaintiffs do not dispute the purity of this starting material. FOF 1013-1014.

Dr. Steed verified that the WI scientists faithfully followed the synthetic procedure set forth in step 3 of Example 25. FOF 1020-1021. As a result, they observed tapentadol hydrochloride that "crystallised out" exactly as described in Example 25. FOF 1021. The product was a white solid, which is how Plaintiffs describe the compound in FDA filings. FOF 1022, 1053. The Wisconsin scientists used XRPD to determine the crystal form which showed at least some Form A. FOF 1024. Importantly, Plaintiffs do not dispute that the Wisconsin reproduction faithfully carried out the third step of Example 25. FOF 1015-1016.

Plaintiffs have only one criticism: the Wisconsin reproduction was purportedly flawed because it should have started with step 1, not step 3. FOF 1014, 1016. Plaintiffs' sole argument, however, was debunked at trial by Plaintiffs' own witnesses. *First*, named inventor Dr. Buschmann admitted that so long as the correct starting material was confirmed for step 3, then the procedure is considered faithfully followed. FOF 1017. *Second*, step 3 requires putting the starting material into solution, which renders the previous steps irrelevant because crystal formation happens *later* in the process. FOF 1009-1010. Drs. Bernstein and Buschmann confirmed that the final crystallization (*i.e.*, going from solution to solid) determines the polymorph, not the solid form used to start the process. FOF 1014 and 1017. *Third*, Plaintiffs' chemistry expert, Dr. Roush—who espoused the argument that a “faithful reproduction” had to start at step 1—could not point to any single reason that any previous step mattered to the issue at hand. FOF 1016. Similarly, Plaintiffs' polymorph expert, Dr. Bernstein, had no opinion about why or how starting earlier in the process would have effected polymorph formation. FOF 1014. *Fifth*, Dr. Bernstein also conceded that no one in this case has ever even theorized that impurities could result in Form A. FOF 1071. So even if Wisconsin's samples were somehow impure, that would only explain why they obtained some Form B, and could not be the but-for cause for the presence of Form A in the sample. For all these reasons, Dr. Steed's thorough explanation and testimony about the prior art resulting in Form A proves inherent anticipation by the requisite clear and convincing evidence. FOF 1079.

3. **Plaintiffs admit that following Example 25 results in Form A.**

In addition to the test results, Example 25 results in Form A by Plaintiffs' own statements in the '364 patent. Example 2 of the '364 patent states that it used starting material “prepared according to example 25,” *i.e.*, Form B. FOF 1024. That starting material was in fact Form A, a

fact confirmed by contemporaneous documents. FOF 1025-1028. Therefore, taking Plaintiffs' own statement at face value, Example 25 results in Form A. FOF 1029.

B. Plaintiffs never actually tested Example 25 as written.

To rebut a finding that Example 25 always results in some Form A and inherently anticipates the '364 patent, Plaintiffs point to three other supposed replications. Yet, none of them actually followed the critical step 3 of Example 25. This is not disputed. Instead, Plaintiffs presented uncorroborated and unconfirmed speculation from their experts that the differences between step 3 in Example 25 and Plaintiffs' employees' actual experiments did not matter. But the experimental differences make all the difference to the accuracy of the reproductions.

1. Buschmann's batch 00 did not follow Example 25 and batch 01 was not tested for polymorphs.

Inventor Dr. Helmut Buschmann flatly admitted that he never synthesized tapentadol hydrochloride in the manner set forth in Example 25, and that the example must have been a "compilation" of different experiments. FOF 1031, 1034-37.⁶ For purposes of proving inherent anticipation, Dr. Buschmann's admission is critical because it shows that the inventors of the '364 patent have no basis for stating that Example 25 results in only Form B tapentadol.

Dr. Buschmann synthesized tapentadol hydrochloride for the first time in 1994. FOF 1030. The first batch was called batch 00. *Id.* Drs. Buschmann and Roush admitted that his batch 00 was *not* made according to Example 25. FOF 1031. The unfaithful reproduction of Example 25 was flawed at least because the product did not have a proper "melting point" as required by Example 25, and had instead a "sintering" point of 123°C, which is way off from the 199-200°C

⁶ That still does not explain why very detailed numbers and procedures were identified in the patent, which would ordinarily be grounds for inequitable conduct. *Novo-Nordisk Pharm. v. Bio-Tech Gen. Corp.*, 424 F.3d 1347, 1357 (Fed. Cir. 2005).

expected for tapentadol, indicating an impure sample. FOF 1032. Any testing of batch 00 is also suspect because of its long and unknown storage history. FOF 1039-1041.

Dr. Buschmann synthesized a second batch of tapentadol hydrochloride in 1994—batch 01. FOF 1030, 1033. But that sample was never tested for its crystal form. *Id.* Therefore, Plaintiffs cannot rely on batch 01 to rebut Defendants’ proof of inherent anticipation because no one knows if it resulted in Form A or B.

2. **The Mueller samples were not faithful to Step 3 of Example 25.**

In 2002, Grünenthal selected technician Marita Mueller to reproduce Example 25. FOF 1042. Ms. Mueller did not have a Ph.D., and her synthetic chemistry experience was limited. FOF 1042-1043. Ms. Mueller crucially did not follow Step 3 of Example 25—the only step where tapentadol hydrochloride crystals are made—and thus are not faithful reproductions. FOF 1044-1045. Based on Ms. Mueller’s mistakes, a person of skill would not have considered her work to be within the scope of Example 25. *See Glaxo, Inc. v. Novopharm Ltd.*, 830 F.Supp 871, 877 (E.D.N.C. 1993) (key consideration is whether “experiment would . . . be considered by a chemist skilled in the art to be within the teachings of” the prior art), *aff’d*, 52 F.3d 1043 (Fed.Cir.1995). Ms. Mueller’s attempted reproductions do not rebut inherent anticipation.

Dr. Steed explained the series of mistakes that Ms. Mueller made in connection with Step 3 of Example 25, and also is the only expert who explained why these mistakes mattered. FOF 1046-1059. *First*, Ms. Mueller, unlike the WI scientists, did not confirm the chemical purity of her starting material. FOF 1046. *Second*, Ms. Mueller did not use the amounts recited in Example 25. FOF 1056. *Third*, Ms. Mueller’s notebooks do not identify the pH that she obtained to make sure that she had achieved an “alkaline” solution as required by the prior art. FOF 1047. *Fourth*, after the extraction step, Ms. Mueller did not properly dry “over sodium sulfate,” but

instead Ms. Mueller simply filtered the material through sodium sulfate. FOF 1048-1049. *Fifth*, Ms. Mueller failed to premix the “trichlormethylsilane/water” before the final recrystallization and instead added them separately. FOF 1050-1052. Dr. Steed explained that these mistakes introduced impurities, including a bromide impurity, into the resulting tapentadol, as confirmed by contemporaneous Grünenthal documents. FOF 1050, 1053-54.

Due to all these errors, Ms. Mueller did not obtain crystals when Example 25 says the product “crystallized out.” FOF 1051, 1055, 1056, 1058. Ms. Mueller had to add a new step not disclosed in Example 25 to get crystals. *Id.* Furthermore, the crystals she obtained were colored, ranging from “mustard yellow” to “beige.” FOF 1052, 1056, 1058. Tapentadol hydrochloride is white. FOF 1053. As Drs. Steed and Matzger explained at trial, the discolored products provide further evidence that Ms. Mueller’s mistakes resulted in impurities. FOF 1052, 1059.

C. Form B samples that persist at room temperature are stabilized by impurities.

The presence of impurities in Ms. Mueller’s experiments is critically important because, as many contemporaneous Grünenthal documents confirmed, only impure samples persist as Form B tapentadol at room temperature. FOF 1070-1078. There is no dispute that Form A is the form of tapentadol that is thermodynamically stable at room temperature. FOF 1060-1064. Dr. Steed explained that a chemically pure sample of Form B will necessarily and inevitably convert to Form A at room temperature as a matter of scientific principle. FOF 1065-1067. That is why, without impurities present, simply cooling Form B to room temperature converts it back to Form A. FOF 1066, 1068-1069.

Grünenthal’s scientists, including inventor Dr. Fischer, recognized that impurities explained why some samples of tapentadol appear to persist as Form B at room temperature. FOF 1071. In a reports prepared by Grünenthal, impurities were repeatedly identified as a likely

reason for the crystallization of Form B while ruling out the existence of a third polymorph. FOF 1060, 1072, 1077. These concerns were later confirmed by third party testing by Crystallics. FOF 1078.

Dr. Bernstein further testified that “if [Form B] is due to impurities, you have to show which impurities and what the level is.” FOF 1075-76. Yet that is exactly what at least one 2003 Grünenthal report sets forth: which impurities matter and at what levels. *Id.* Grünenthal also identified bromide as a likely stabilizing impurity, and Dr. Steed explained how Ms. Mueller’s mistakes incorporated bromide into her final products. FOF 1073-1074.

If there is any doubt about whether Ms. Mueller’s replication can be explained in view of the impurities that it had, that doubt should be resolved in Defendants’ favor because—through no fault of Defendants—her samples no longer exist. FOF 1054. Plaintiffs destroyed the samples, so that they are unavailable for purity testing and other chemical characterization to show just how and where Ms. Mueller’s mistakes resulted in an impure result. In contrast, the Wisconsin scientists’ work was available to anyone in this case who wanted to test it, and is therefore a more reliable test to fairly represent what happens when one follows Example 25 properly.

III. THE ASSERTED CLAIMS OF THE ’364 PATENT ARE INVALID AS OBVIOUS

Even if not anticipated, the asserted claims for Form A tapentadol would have been obvious in view of the ’737 patent in combination with common knowledge in the field about polymorph screening such as found in the FDA Guidance and Byrn article. FOF 1503-1504. Inventions are invalid as obvious under 35 U.S.C. § 103 when “the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a [POSA] to which said subject matter pertains.” *KSR Int’l Co. v. Teleflex, Inc.*, 550 U.S. 398, 406 (2007) (citation and quotation

marks omitted).⁷ Obviousness is proven by showing that no more than ordinary skill and routine experimentation is required to achieve the supposed invention. *Merck & Co., Inc. v. Biocraft Labs, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989) (claimed combination was obvious because it was “reached by means of routine procedures”). As detailed below, Grünenthal did nothing more than follow routine procedures to get Form A, as any POSA would have done, and for which a patent monopoly is not warranted.

A. Grünenthal hired contract lab for standard polymorph screen following the established protocol published in the prior art.

Grünenthal’s alleged discovery of Form A was obvious because it was the result of a standard polymorph screen, which drug developers were taught to do by the prior art. Tapentadol hydrochloride was disclosed as a new drug in the ‘737 patent. FOF 1501. The ‘737 patent even reported that tapentadol solid was crystalline in nature, since following the recipe to make it resulted in solid material that “crystallised out.” FOF 1502. Well before the ‘364 patent application date, tapentadol in particular had been selected and identified in the World Health Organization listing which identified tapentadol as a drug used as an analgesic. FOF 1501. The only thing people had not yet tested was whether tapentadol had one crystal form or multiple crystal forms, known as polymorphs. FOF 1502.

The prior art motivated drug companies to investigate polymorphism for any new drug and also told them how to do a polymorph screen. As far back as 1987, the FDA issued a guidance document that specifically told companies that “[s]ome drug substances exist in several different crystalline forms (‘polymorphs’).” FOF 1503. The FDA therefore directed companies

⁷ There is little dispute among the expert witnesses as to the definition of a POSA. Drs. Steed, Matzger, and Bernstein all applied a definition that included a Ph.D. in chemistry or related field or a lower degree with additional work experience. (FOF ____). To the extent there are any wording differences, they do not alter the obviousness analysis.

that “[a]ppropriate analytical procedures should be used to determine whether (or not) polymorphism occurs.” *Id.* As Dr. Steed explained, it was well known in the prior art and the FDA Guidance confirmed that any drug developers should investigate polymorphism. FOF 1503. Even named inventors Drs. Gruss and Buschmann admitted that the FDA Guidance compelled Grünenthal to investigate polymorphs of tapentadol. FOF 1503, 1506.

While 2001 allegedly was the first time that Grünenthal had encountered or considered polymorphs, FOF 1511, it was certainly not the first time that those of ordinary skill in the art had considered polymorphs. In fact, by 2001 it was common knowledge how to do a polymorph screen. FOF 1513-1518. This information was even summarized in prior art publications, including the 1995 Byrn paper. FOF 1519-1521. In that paper, Dr. Byrn described how one should perform a routine polymorph screen using a list of common solvents and standard techniques like cooling and evaporation. FOF 1521. Indeed, as the introduction to the 1995 Byrn paper makes clear, its whole purpose was to help codify what people of ordinary skill in the art understood were the “appropriate” techniques that the FDA had asked people to investigate pursuant to the 1987 Guidance. FOF 1504. The Byrn paper therefore lays out in plain terms what that means, at least in terms of the very first and therefore the very most obvious steps one would take:

The first step . . . is to crystallize the substance from a number of different solvents in order to attempt to answer the question: Are polymorphs possible? Solvents should include those used in the final crystallization steps and those used during formulation and processing and may also include water, methanol, ethanol, propanol, isopropanol, acetone, acetonitrile, ethyl acetate, hexane and mixtures if appropriate. New crystal forms can often be obtained by cooling hot saturated solution or partly evaporating clear saturated solutions. FOF 1521.

Thus, a POSA following the instructions in the prior art Byrn article pursuant to motivation provided by the FDA's Guidance would have obtained the subject matter of the asserted claims of the '364 patent (Form A) through routine and conventional means. As such, those claims are invalid, as claims are obvious where the experimentation needed to arrive at the claimed subject matter was “‘nothing more than routine’ application of a well-known problem-solving strategy.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1368-69 (Fed. Cir. 2007) (citing *Merck & Co. v. Biocraft Laboratories, Inc.*, 874 F.2d 804, 809 (Fed. Cir. 1989)).

Grünenthal hired a third party, SSCI, to run the routine polymorph screen described in the Byrn reference. FOF 1511-1512. SSCI was known to do this kind of routine work polymorph screen. FOF 1523. In fact, the person who founded SSCI was the very same Dr. Byrn who wrote the prior art instructions for how to conduct a polymorph screen. FOF 1522. And when SSCI did the polymorph screen, they used eight of the nine solvents already published in the Byrn paper (including the isomer of the 9th). FOF 1524-1525. SSCI also varied cooling and evaporation techniques that were expressly directed in the Byrn paper. FOF 1525.

B. All preliminary tests resulted in Form A.

Less than one month after receiving the tapentadol starting material from Grünenthal, SSCI reported its first-pass preliminary results, reflecting the easiest and most obvious crystallization conditions, *i.e.*, the conditions disclosed in the Byrn paper. FOF 1524-1525. Form A was unavoidable. No matter what solvent and no matter what conditions SSCI used from those already published in the Byrn prior art, SSCI always generated at least some Form A tapentadol. FOF 1526. Not surprising given the fact that Form A is the stable form at room temperature. And it is not as if the number of experiments SSCI did was large or exceptional: projected to be 50-70 according to the contract. FOF 1512. Dr. Gruss himself admitted that even 97 experiments was considered a “small number” when it comes to polymorph testing, and would have only been a

“start” that any person would have done. *Id.* In this context, the work that SSCI did could not have been anything other than routine.

Precisely because Form A was so obvious and so easy to make, Grünenthal had to tell the Patent Office that its invention was actually ***starting with Form B*** tapentadol and converting it into Form A. FOF 1024. But as Plaintiffs’ witnesses admitted one after another, and Plaintiffs admitted in their interrogatory responses, they never actually started with Form B. FOF 1026. Instead, the starting material “converted” to Form A in each of Examples 2, 3, 5, 9 and 11 of the ’364 patent—purportedly Form B resulting from Example 25—was actually Form A all along. FOF 1024-1026. The supposed invention touted in the ’364 patent ended up therefore being nothing more than taking Form A tapentadol, dissolving it in solution, running various chemical processes, and then crystallizing the same Form A tapentadol. FOF 1534. That is not worthy of a patent.

C. Even if not predictable, Form A was obvious

Plaintiffs have only one response to the straightforward obviousness analysis that a person of ordinary skill would do a routine screen and inevitably come up with Form A. That response? Dr. Bernstein’s extreme view that no polymorph can ever be obvious because it’s not predictable. FOF 1530. Dr. Bernstein even maintained that view ***even if*** the prior art had specific instructions for a screen, it still wouldn’t be obvious to follow that screen because you wouldn’t know the result ahead of time. *Id.* Such a bright line rule has never been adopted by the courts.

Dr. Bernstein’s extreme view should be rejected, because it does not comport with the fundamental test of obviousness in two respects. First, the standard is not whether one would “know the result ahead of time”; to the contrary, obviousness requires only a “reasonable expectation” of obtaining the claimed subject matter. Thus, “obviousness does not require absolute predictability of success,” but, rather requires “a reasonable expectation of success.” *See*

Medichem, S.A. v. Rolabo, S.L., 437 F.3d 1157, 1165 (Fed. Cir. 2006) (quoting *In re O'Farrell*, 853 F.2d 894, 903-904 (Fed. Cir. 1988)). Obviousness “cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Here, the evidence clearly and convincingly showed that a POSA would have had a reasonable expectation of success in obtaining the thermodynamically stable polymorph (which turns out to be Form A) utilizing the routine screening suggested by the FDA given that the entire purpose of the Guidance was to ascertain the appropriately stable polymorph for use as a pharmaceutical. FOF 1503. The expectation of success was confirmed by the prior art that announced that at least one crystal form of tapentadol hydrochloride existed. FOF 1502.

Second, Plaintiffs ignore that the obviousness inquiry asks what a POSA would have done given the problem to be solved, keeping in mind the common sense and ordinary creativity of POSA. *KSR*, 550 U.S. at 419-420, 421. The problem to be solved was to identify the crystal form already identified and to determine if other crystal forms existed. To address that problem, Grünenthal did nothing more than conduct a standard polymorph screen, following the FDA Guidance and the Byrn paper, just as any POSA would have done. The result of this obvious solution was Form A tapentadol. Thus, Form A is obvious and no patent monopoly is warranted.

Moreover, Form A has not unique or special properties that warrant patent protection. Not only is it the easier form to obtain, but both Form A and B have the same dissolution profile. (FOF 1531), and both have the same biological activity. FOF 1531.

Here, there was far more than a reasonable expectation of success: there was an express disclosure in the ‘737 patent that making tapentadol results in a crystalline form. FOF 1502. As far as determining what that form was, and even assuming it was not Form A, following the

known and established prior art protocol—published in Byrn precisely because it was so likely to result in success—would still have resulted in Form A. FOF 1520-1521. Just as Dr. Steed explained, therefore, a person of ordinary skill in the art would know to run a polymorph screen, and with the guidance of the ‘737 patent and Byrn, a person of ordinary skill would have a reasonable expectation of success to find a stable polymorph at room temperature. FOF 1526. With tapentadol, having only two forms, and only one of them stable at room temperature, the easiest and most obvious tapentadol polymorph one would find is Form A.

Even Dr. Bernstein admitted that “sometimes it’s easier and sometimes it’s more difficult” to find a polymorph. FOF 1532. Grünenthal should not be entitled to a patent on hiring SSCI to do the easy work of following the prior art and finding the one of two possible polymorphs, particularly when Form A is the one that is stable at room temperature.

Accordingly, claims 1-3 of the ‘364 patent which are directed to form A of tapentadol are obvious.

D. Form A in a dosage form with an additive was obvious

Asserted claim 25 is also obvious. A POSA would have recognized that using the more stable form of tapentadol—form A—in a dosage form would have been preferred. Furthermore, the ‘737 patent discloses using form A tapentadol in a dosage form along with an additive or auxiliary substance, rendering claim 25 obvious. FOF 1507-1509, 1528.

IV. THE ‘364 PATENT SPECIFICATION FAILS TO SHOW UTILITY

“The utility requirement of 35 U.S.C. § 101 mandates that any patentable invention be useful” and if “a patent claim fails to meet the utility requirement ... then it also fails to meet the how-to-use aspect of the enablement requirement [of § 112].” *In re ‘318 Patent Infringement Litig.*, 583 F.3d at 1323-24. The patentee is required to show that its invention has “characteristics or qualities of utility that are new and materially different from [that] disclosed

by the art of record.” *Application of Selmi*, 156 F.2d 96, 99 (C.C.P.A. 1946). Whether a patent meets the utility requirement is determined by the information contained in the patent itself. *See Rasmusson*, 413 F.3d at 1323. Where there is “no indication that one skilled in the art would accept without question statements as to the [asserted] effects . . . and no evidence has been presented to demonstrate that the claimed products do have those effects,’ an applicant has failed to demonstrate sufficient utility[.]” *Rasmusson*, 413 F.3d at 1323. (COL 501-09, 2001-04.)

A. The Statement of Utility is Inherently Vague and Insufficient

The ’364 Patent’s lone contention of utility is that the claimed “Crystalline Form A . . . has the same pharmacological activity as Form B but *is more stable under ambient conditions*.” (FOF 2001, 2002.)⁸ That statement is so inherently vague it is “meaningless.” *In re Fisher*, 421 F.3d 1365, 1377 (Fed. Cir. 2005). There is no definition of “ambient conditions,” which could mean humidity and/or pressure and/or temperature. (FOF 2006.) Nor does the patent define “stability.” (FOF 2007.) “Stability” could denote form hydration stability, a major issue in pharmaceuticals, which concerns the propensity of a polymorph to incorporate water or solvent atoms within its lattice. (FOF 2008.) Or it could refer to chemical stability which is the propensity of certain polymorphs to degrade into other chemicals, a property linked to shelf-life. (FOF 2009.) Last, “stability” could refer to thermodynamic stability which relates to the solid-solid conversion between crystal structures. (FOF 2010). Dr. Bernstein agreed “stability” was

⁸ This is the assertion of utility against which the patent must be measured. *See Rasmusson*, 413 F.3d at 1323; *see also In re Kirk*, 375 F.2d 940 (C.C.P.A. 1967). Plaintiffs wrongly suggested for the first time at trial that the methods of preparing/ characterizing Form A could be a basis for utility. First, that contention is not set forth in Plaintiffs’ discovery responses, PTO or Pre-Trial Brief, and therefore has been waived. *See* Plaintiffs Pretrial Brief at 24; Joint PTO at ¶ 717-720; *Krys v. Aaron*, 312 F.R.D. 373, 376 (D.N.J. 2015); (FOF 2001.) Second, the lone asserted utility in the specification is Form A itself. (FOF 2001.) Third, a process for making a product not yet itself shown useful cannot meet the utility requirement. *See Brenner v. Manson*, 383 U.S. 519, 534, 86 S. Ct. 1033, 1041-42(1966). (COL 2005)

inherently vague. (FOF 2011.) Dr. Matzger's unrebutted testimony shows that, without further information, one skilled in the art is not able to determine even what type of stability Form A allegedly had over Form B. (FOF 2003, 2012.) Further, there is no data in the specification demonstrating that Form A is more stable using *any* of those types of stability. (FOF 2012.) Absent data, a POSA would not accept without question that conclusory statement, because the polymorphs properties are unpredictable. (FOF 2013.)

B. Thermodynamic Stability Still Has No Demonstrated Utility

Greater thermodynamically stability does not demonstrate stability, given the total lack of information in the patent specification regarding Form A. (FOF 2022.) It was undisputed that greater stability does not necessarily demonstrate utility in a drug; sometimes the opposite is true. (FOF 2014, 2015.) As Dr. Matzger testified, in many instances a less stable form is desired for pharmaceutical compositions because it will exhibit favorable dissolution behavior. (FOF 2015.) Grünenthal's Dr. Gruss and Plaintiffs' expert Dr. Bernstein agreed that greater thermodynamic stability is often disfavored for drugs. (FOF 2016-18.) There is nothing in the patent to prove greater stability would be useful. (FOF 2020.) Drs. Matzger and Bernstein agree that "there is no way to predict whether the most stable form will be sufficiently soluble, bioavailable, or processable to perform adequately in a pharmaceutical product" without bioavailability or solubility tests. (FOF 2019.) But there is *no* solubility or bioavailability data in the patent. (FOF 2021.) Without such data, the recited stability is meaningless, and Form A is "an invention that is simply an object of research." *In re '318 Patent Infringement Litig.*, 583 F.3d at 1324. (FOF 2022.) In any event, Grünenthal's internal testing, not disclosed, shows there is no material difference in the usefulness of Form A and Form B. (FOF 2021.)

C. There Is Insufficient Data to Determine the Thermodynamic Stability at Pertinent Temperatures

Further, the patent contains *no data* demonstrating alleged greater stability at any condition that matters. (FOF 2024.) One skilled in the art would not accept without question the alleged greater stability of Form A, but would require data proving it. (FOF 2026.) The patent contains no solubility data, the gold standard in showing thermodynamic stability, nor any other data, proving that Form A is more stable than Form B at ambient (or any other) conditions. (FOF 2024.) The documentary evidence confirms that scientists in the field deem relative solubility data as the key indicator of thermodynamic stability. (FOF 2023.) Further, a person skilled in the art reading the patent does not know the thermodynamic stability at room temperature (22 °C/72 °F) or body temperature (37 °C/98.6 °F); the two pertinent temperatures for drugs. (FOF 2026.)

Dr. Bernstein relied exclusively on Example 16 for alleged data to support utility. (FOF 2025.) But Example 16 does not contain solubility data, which is what a POSA would need to see for thermodynamic stability. Example 16 merely states that an experiment was run where “Form A converted to Form B from 40-50 °C [i.e., 104-122 °F]” and “the result is reversible with Form B changing over into Form A at a lower temperature.” (FOF 2025.) Contrary to Dr. Bernstein’s blind assumption, a POSA would not regard that statement as supporting the asserted utility because the ostensibly “lower” temperature is not specified and the bald statement is not “data” in any event, let alone data showing that Form A is “more stable under ambient conditions.” *Rasmusson*, 413 F.3d at 1323 (FOF 2025, 2026.)

In sum, Defendants have proven by clear and convincing evidence that the ’364 Patent fails to meet the requirements of 35 USC §§ 101, 112, rendering the asserted claims invalid. (FOF 2027.); (COL 2006.)

V. THE '364 PATENT IS UNENFORCEABLE BECAUSE OF UNCLEAR HANDS

A court of equity may dismiss a cause of action “where some unconscionable act of one coming for relief has immediate and necessary relation to the equity that he seeks in respect of the matter in litigation.” *Keystone Driller Co. v. Gen. Excavator Co.*, 290 U.S. 240, 245 (1933). Unclear hands may render a patent procured by misconduct in the PTO unenforceable. ECF No. 392; *see also Monsanto Co. v. Rohm & Haas Co.*, 456 F.2d 592, 598 (3d Cir. 1972). “Bad faith may be established by circumstantial evidence and each case must depend upon its peculiar facts.” *Bankers Trust Co. of Western N.Y. v. Crawford*, 781 F.2d 39, 44 (3d Cir. 1986). (COL 2007-09.)

Grünenthal’s misconduct was the fundamental reason the PTO granted the ’364 patent. Grünenthal prominently told the PTO that “the present invention provides a new form (Form A) . . . which is different from the form already known (Form B) ***obtained by the procedure described in example 25***” of the prior art. (FOF 2028). The Examiner expressly relied on that statement and corresponding portions of the specification in granting the patent. (FOF 2029.) But the ’364 patent contains *no* data whatsoever that corresponds to Example 25. (FOF 2033.) Instead, Grünenthal misled the PTO into concluding that Examples 7 and 10 and Figures 4 and 8 correspond to Form B prepared according to Example 25. (FOF 2030-33.) Example 7 recites that Form B(1) is made by the procedure described in Example 25 and Example 10 is the XRPD of B(1). (FOF 2030.) Plaintiffs admitted that Figure 4 does not correspond to Example 25. (FOF 2033.) The patent indisputably discloses no data at all for Form B produced by Example 25. (FOF 2033.)⁹

⁹ Applicants were aware that an XRPD of Tapentadol made according to Example 25 would not, in fact, look like the pattern depicted in Figure 4 given the odd synthesis of CEP11a, which was the basis for Figure 4, and since the re-creations of Example 25 attempted by Grünenthal showed signs of incorporated impurities. (FOF ¶¶2033, 2035.) These recreations are also inherently

Form A was the ubiquitous form present in samples synthesized at Grünenthal. Both Grünenthal and SSCI had difficulty even making a relatively stable Form B. (FOF 2035.) To make Form B stable at room temperature, Grünenthal had to incorporate impurities or mill the product. (FOF 2035.) Grünenthal disclosed none of this information to the PTO but rather wrongly erroneously characterized Form A as the “new form.” (FOF 2036.)

Additionally, certain examples of the '364 Patent were never performed by Grünenthal as represented. (FOF 2037-40.) Those examples were supposedly methods of preparing Form A that allegedly started with Form B prepared according to Example 25. (FOF 2037-38.) These assertions were false; rather, Form A itself was the starting material. (FOF 2038.) In short, Grünenthal told the Patent Office that their invention was making Form A from Form B, when in fact they had made Form A from Form A. (FOF 2038.) Plaintiffs do not deny this; their only excuse is that the starting material allegedly “doesn’t matter.” (FOF 2039.) Apart from the fact that this is totally inconsistent with Plaintiffs’ criticism of University of Wisconsin recreation, *see disca. supra*, even had the nature of the starting material been irrelevant, it would have mattered to the Examiner, who stated he was relying on the statements in the specification in issuing the patent. (FOF 2029.)¹⁰

In sum, Grünenthal consciously hid from the PTO a multitude of data that was directly at odds with its representations to the PTO Examiner that their alleged invention was novel. (FOF 2028, 2041-42.) The cumulative effect of all of their misstatements and omissions is more than enough circumstantial evidence for the Court to infer Grünenthal’s intent to mislead the PTO.

suspect since when Ms. Mueller was asked to perform Example 25 for the *first* time, she was told to enter in her lab notebook that the result was Form B *before* the sample results had even come back. (FOF 2034.)

¹⁰ Lastly, Dr. Matzger testified (unrebutted) that several of the examples falsely claim to have the final results confirmed by RAMAN microscopic analysis (a technique that can show impurities). (FOF 2040.)

(COL 2010.) See *Ohio Willow Wood Co. v. Alps S., LLC*, 813 F.3d 1350, 1359 (Fed. Cir. 2016) (inferring deceptive intent from misrepresentations and omissions to the PTO). Plaintiffs are precluded from enforcing the ‘364 Patent. (COL 2010.)

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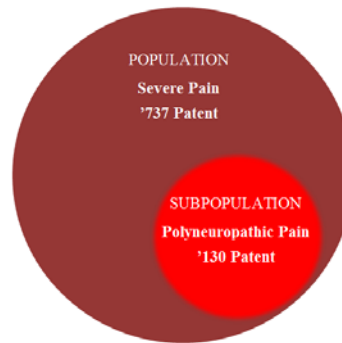
VII. THE CLAIMS OF THE '130 PATENT ARE ANTICIPATED BY THE '737 PATENT

U.S. Patent No. 6,248,737 (DTX 752; “the ’737 patent”) issued on June 19, 2001, more than one year before the March 2007 filing of the earliest application to which the claims of the ’130 patent may claim priority. (FOF 3501.) Thus, the ’737 patent is prior art to the claims of the ’130 patent under 35 U.S.C. § 102(b).

Example 25 of the ’737 patent discloses tapentadol hydrochloride, and describes it and related compounds as being “suitable for the treatment of severe pain.” FOF 3502. The ’737 patent describes a method of administering tapentadol hydrochloride to a subject, just as in the claims of the ’130 patent. (FOF 3503.)

Each of the experts, including Plaintiffs’ expert Dr. Brown, agreed at trial that the population of patients with “severe pain” includes those with polyneuropathic pain. Indeed, this is the crux of Plaintiffs’ infringement allegations against Actavis and Roxane. Although the ’737 patent does not expressly state that some of the population with severe pain will suffer from

polyneuropathic pain, some of the population with severe pain will necessarily include a subpopulation with polyneuropathic pain. (FOF 3504-3507.)



“[A] prior art reference may anticipate without disclosing a feature of the claimed invention if that missing characteristic is necessarily present, or inherent, in the single anticipating reference.” *Schering*, 339 F.3d at 1377.

In another Hatch-Waxman case in this district, Judge Greenaway concluded that a prior art method of treating all patients with allergies necessarily included a method of treating allergy sufferers with hepatic impairment, which anticipated a later patent claim to a method of treating allergies in patients with hepatic impairment. *Aventis Pharmaceuticals, Inc. v. Barr Laboratories, Inc.*, 411 F.Supp.2d 490, 522 (2006) (“use of the same method, for the same purpose, on a subgroup of an old group will not be patentably new.”).

Aventis v. Barr	'130 patent
PATENTS-IN-SUIT CLAIMS Methods of administering antihistaminic amount of fexofenadine to hepatically impaired allergic patients	'130 PATENT CLAIMS Methods of treating polyneuropathic pain by administering tapentadol
PRIOR ART Methods of treating allergic reactions by administering fexofenadine	PRIOR ART '737 patent: Example 25 discloses tapentadol hydrochloride as “suitable for the treatment of severe pain”

Aventis v. Barr	'130 patent
<p>CONCLUSION</p> <p>Prior art and patents-in-suit: Same method of administering fexofenadine</p> <p>Prior art: Directed to all allergy patients</p> <p>Patents-in-suit: Address subpopulation of allergy sufferers</p> <p>Same method, same purpose, subgroup of an old group = inherently anticipated</p>	<p>CONCLUSION</p> <p>Prior art and '130 patent: Same method of administering tapentadol</p> <p>Prior art: Directed to all chronic and/or severe pain patients</p> <p>'130 patent: Addresses subpopulation of polyneuropathic pain</p> <p>Same method, same purpose, subgroup of old group = inherently anticipated</p>

Likewise here, the same method and purpose recited in the claims of the '130 patent are described in the '737 patent, namely administering tapentadol hydrochloride to treat pain. And the population in the '737 patent (those with “severe pain”) includes the subgroup of those with polyneuropathic pain.

VIII. THE ASSERTED CLAIMS OF THE '130 ARE INVALID FOR OBVIOUSNESS-TYPE DOUBLE PATENTING

The supposed invention in the '130 patent is to use tapentadol to treat diabetic polyneuropathy (“DPN”), a form of polyneuropathic pain. But tapentadol is admittedly a derivative of tramadol—both are dual-acting opioids—and the prior art already showed tramadol’s efficacy specifically for DPN. Moreover, tapentadol was already disclosed in the prior art to treat severe pain, which includes polyneuropathic pain and DPN. Grünenthal is not entitled therefore to multiple patents that cover the same drug for the same use: under the law of obviousness-type double patenting, the '130 patent claims are invalid.

The '593 prior art patent, which Grünenthal owns, is due to expire in 2022. FOF 4004. The '130 patent, which Grünenthal commonly owns, is due to expire in 2028, providing it six additional years of patent monopoly. FOF 4004-05. Under the law of obviousness-type double

patenting, Grünenthal is prohibited from “obtaining more than one patent on the same invention.” *AbbVie Inc. v. Kennedy Inst.*, 764 F.3d 1366, 1373-74 (Fed. Cir. 2014). The public has the right to use the ‘593 patent and its obvious derivatives, because “the ban on double patenting ensures that the public gets the benefit of the invention after the original period of monopoly expires.” *Id.*

The ‘593 patent, claim 117, already disclosed and claimed the use of tapentadol hydrochloride in particular for “treating a mammal suffering from pain.” FOF 4006. The ‘593 patent also explains that the type of pain to be treated is “severe pain.” FOF 4014. Both Dr. Brown and Dr. Buvananedran agree that “severe pain” as of the time the ‘130 patent was filed, would naturally include both nociceptive and neuropathic pain. FOF 4011-13. Dr. Brown even argues that Defendants infringe simply by referring to “severe pain” because that is enough instruction to use tapentadol for polyneuropathic pain in particular. FOF 4014. Plaintiffs cannot have it both ways: if “severe pain” is specific enough to include DPN in Defendants’ labels, then it is enough to include DPN in the prior art.

At trial, therefore, Dr. Brown disputed what a POSA would understand “severe pain” to mean in 1994, and argued that it included only nociceptive pain and not neuropathic pain. She offered no evidence to support this assertion. Dr. Ossipov made the same assertion at trial, but again without evidence. The only evidence for the understanding of pain at that time is the Hammond reference, which showed that pain includes both nociceptive and neuropathic pain. FOF 4015-17. In any event, Plaintiffs used the wrong timeframe for the obviousness analysis. The question for obviousness-type double patenting is what would have been obvious to a POSA as of the time of the ‘130 patent application, which was not filed until 2007. FOF 4022; *Amgen Inc. v. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1355 (Fed. Cir. 2009).

If a later issued patent claims a method of using a compound described in an earlier issued patent, then that later claim is invalid. *Sun Pharm. Indus., Ltd. v. Eli Lilly & Co.*, 611 F.3d 1381, 1385 (Fed. Cir. 2010). A POSA would understand the disclosure of treating “pain” with tapentadol in claim 117 of the ’593 patent, as treatment of each of the four main subcategories of pain, including polyneuropathic pain. FOF 4018-19. And among polyneuropathic pain, DPN is a predominant. Thus, the asserted claims of the ’130 claim methods of using tapentadol described in the earlier issued ’593 compound. FOF 4018, 21. As such, the claims are invalid as a matter of law. *Sun*, 611 F.3d at 1385-86, 1389.

But even if Dr. Brown’s analysis were correct, and “severe pain” in the ’593 patent meant only nociceptive pain, then that still does not overcome obviousness. It was entirely obvious to treat neuropathic pain in view of the ’593 patent disclosures that it was used to treat “severe pain,” that “opioids have been used for many years as analgesics,” and that the expected goal for tapentadol was to use it as any other opioid but “without giving rise to the side effects which are typical of opioids.” FOF 4014, 22. Given the abundance of literature showing that tramadol and opioids generally had been used to treat neuropathic pain and DPN in particular, the obviousness of using tapentadol to treat DPN cannot be seriously disputed. FOF 4024; 4025-27 (Grünenthal internal reports); 4028-34 (tramadol); 4035-38 (morphine); 4039-44 (treatment algorithms); 4045-47 (literature reviews); 4048 (clinical practice). The Harati reference, for example, was even titled “Double-blind randomized trial of tramadol for the treatment of the pain of diabetic neuropathy.” FOF 4028. It was known that tapentadol was a tramadol derivative (FOF 4022-23), that tapentadol worked to treat pain (FOF 4014), and that opioids were used for polyneuropathic pain. FOF 4024-48. Claims 1, 2, 3, and 6 of the ’130 patent therefore at least cover an obvious variant of claim 117 of the ’593 patent. The prior art as a whole would motivate a POSA to at

least try tapentadol in an animal model of polyneuropathic pain and to expect success. FOF 4052. Dr. Brown only offered opinions about the use of tapentadol in humans; she is not an expert in animal models. FOF 4050. And Dr. Ossipov offered no opinions regarding the prior art of the clinical use of opioids to treat polyneuropathic pain. FOF 4051.

Even the PTO agreed that the ‘130 patent was obvious, in view of the ‘737 patent —the patent from which the ‘593 patent reissued. The PTO focused on the disclosure of the ‘737, whereas the OTDP analysis here focuses on the claims of the ‘593 patent. FOF 4053. The PTO issued multiple rejections confirming that the ‘593 patent already disclosed tapentadol for the “**treatment of severe pain**,” which included DPN. *Id.* (bold in original).) Yet Dr. Brown did not testify about the prosecution history and did not even recall reviewing the PTO’s invalidity assessment. FOF 4054. As Plaintiffs’ own counsel pointed out during cross examination of Dr. Buvanendran, the PTO agreed with him about the obviousness of the claimed invention. FOF 4055. That makes it a case of “prima facie” obviousness, meaning that the prior art disclosed the claimed invention. The obviousness-type double patenting analysis can stop there. *Geneva Pharm. v. GlaxoSmithKline*, 349 F.3d 1373, 1378 (Fed. Cir. 2003).

Because the prior art showed prima facie obviousness, Grünenthal resorted to submitting a declaration to the PTO alleging that there were “unexpected and surprising extreme and selective effectiveness of tapentadol” that “effectively rebuts such *prima facie* obviousness.” FOF 4053. In support, Grünenthal submitted the declaration of Dr. Christoph, which he argued shows that tapentadol is more selective than morphine for treating polyneuropathic pain. *Id.* Though this is disputed, even taking Dr. Christoph’s declaration at face value, there are three reasons it is inconsequential. *First*, it does not show anything was “unexpected,” and merely reports results of some tests, and Dr. Brown admitted there were no original expectations that

tapentadol should not work. FOF 4061-64. Second, all of the evidence since the declaration shows that tapentadol really is not any more helpful than other prior art, showing that there were no unexpected “benefits.” FOF 4065-69. *Third*, Dr. Christoph compared tapentadol to morphine, when he should have compared it to tramadol, the closest prior art. FOF 4056-59. Dr. Brown admitted comparing tapentadol to morphine is “unfair” since it is not a dual-action drug, and Dr. Roush even put morphine in a different galaxy than tramadol, showing it was not a proper comparator. FOF 4059.

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Respectfully submitted,

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CERTIFICATION OF SERVICE

I hereby certify that on April 18, 2016, a copy of the foregoing DEFENDANTS' POST TRIAL BRIEF was served by notice of electronic filing and electronic mail upon all counsel of record.

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